Symposium article

Quality of life studies and genito-urinary tumors

O. Bertetto,1 S. Bracarda,2 M. Tamburini3 & E. Cortesi4

1Medical Oncology Division, Le Molinette Hospital, Turin; 2Medical Oncology Division, Policlinico Hospital, Perugia; 3Psychological Research Division, National Tumor Institute, Milan; 4Department Experimental Medicine and Pathology, Medical Oncology, University of Rome 
'La Sapienza'; Rome, Italy

Summary

Background: Genitourinary (GU) tumors represent a large proportion of solid cancers (1 of 4) and a wide variety of natural histories, based on various prognostic factors and resulting in different treatment options and end points. In some cases, for the same stage of disease, different treatment strategies do not impact differently on overall survival (OS): surgery vs. radiation, or radical vs. conservative multidisciplinary approach, adjuvant or neoadjuvant, chemotherapy vs. BSC. Quality of life (QoL) is considered a reasonable end point when differences in OS do not seem to be striking.

Design: A review of the literature on different disease stages was undertaken to show where and when QoL was used as the end point of treatment efficacy.

Results: Very few studies have been performed in prostate, bladder and testicular cancer to show the impact of different treatment approaches on QoL. Although these studies might be considered as non-conclusive, some data may allow a better choice for the patients.

Conclusions: QoL as the principal end point has not been used in clinical trials of GU tumors comparing different treatment approaches. This makes the choice between treatments offering similar survival but different toxicity patterns, body and behavioral consequences more difficult. We suggest that future prospective randomized studies should be planned taking into account the QoL as the main end point.

Key words: genito-urinary tumors, quality of life

Introduction

Patients affected by genitourinary tumors frequently receive, for the same stage of disease, different treatment options with similar results regarding activity, efficacy and survival, but with different profiles of short- and long-term toxicities.

Cancer patient concerns about the quality of life (QoL) have certainly been increasing in recent years. It is therefore more and more important for urologists and medical oncologists to be able to advise patients about the various related issues, based on solid data derived from comparative trials in which QoL is the main object of the study.

Unfortunately few such studies have been conducted. The literature on QoL and genitourinary tumors offers a great mass of data from which some conclusions might be drawn. Caution must be exercised so that data on efficacy and toxicity are not directly translated into QoL as perceived by patients, and efforts must be made to interpret the results of the studies on QoL within the treatment options that we currently offer to our patients.

Localized prostate cancer (T1-2, N0, M0)

The diagnosis of localized prostate cancer has become more frequent in recent years, as a consequence of the large diffusion of prostate-specific antigen (PSA) testing [1]. Treatments of choice for intracapsular disease are radical prostatectomy (RP) and radical radiotherapy (RR), while brachytherapy and watchful waiting are reported as possible options only in selected cases identified on the basis of the most important prognostic factors: Gleason Score, clinical stage and baseline PSA [2, 3]. The primary end point in the treatment of localized prostate cancer is overall survival (OS) but, even if similar results between RP and RR have been reported, no prospective randomized study comparing both clinical results and quality of life (QoL) exists. Some of the most interesting published studies [3–8], mainly retrospective and evaluating only clinical or QoL factors, are reported in Tables 1 and 2. An analysis of these studies confirms a substantial equivalence in OS between RP- and RR-treated patients but also a slight trend in favor of RP (vs. RR) in patients with high-risk disease (stage T2b, Gleason score 7–10, baseline PSA: >20 ng/ml). Both high- and intermediate-risk patients (stage T2b, Gleason score 5–6, baseline PSA: 10–20 ng/ml) seem to have better OS if treated with RP or RR vs. brachytherapy [3, 5]. Understanding the similar OS but the different patterns of toxicity, as shown from the QoL evaluation after RP and RR (more incontinence and impotence after RP, more gastrointestinal toxicity after RR, no difference for general health perception and psychological status), a patient and his physician
Table 1. Studies and their clinical end points.

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>No. patients</th>
<th>End point</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>D'Amico [4]</td>
<td>RP vs. RT vs. Br (retrospective)</td>
<td>1872</td>
<td>PFFS (five years)</td>
<td>No difference in low-risk patients RP/RT better than brachytherapy in high- and intermediate-risk patients</td>
</tr>
<tr>
<td>Kupelian [5]</td>
<td>RP vs. RT (retrospective)</td>
<td>551</td>
<td>PFFS (five years)</td>
<td>PFFS (%) L. Risk (%) H. Risk (%) RP 43 80 37 RT 57 81 26</td>
</tr>
</tbody>
</table>

Table 2. Studies with end-point QoL.

<table>
<thead>
<tr>
<th>Study design</th>
<th>No. patients</th>
<th>Instrument</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shrader-Bogen [6]</td>
<td>RP vs. RT</td>
<td>274</td>
<td>FACT G PCTO Q FACT scores comparable</td>
</tr>
<tr>
<td>Lilleby [7]</td>
<td>RP vs. RT</td>
<td>262</td>
<td>EORTC QLQ C30 No difference compared to an age-matched population</td>
</tr>
<tr>
<td>Clark [8]</td>
<td>(Phase III)</td>
<td>250</td>
<td>IPSS SF 36 No difference</td>
</tr>
</tbody>
</table>

Abbreviations: Br - brachytherapy; PFFS - PSA failure-free survival.

could opt for the most appropriate potential and curative treatment on the basis of prognostic factors, age, toxicity profile and individual preference.

Advanced prostate cancer

The treatment of choice for advanced (N+ and/or M+) prostate cancer is androgen ablation, which can be achieved with orchiectomy or luteinizing hormone-releasing hormone (LH-RH) analogues ± peripheral antianrogen. The treatment is effective in 80%–85% of patients. The selection of the most appropriate treatment (monotherapy or complete androgen blockade, CAB) could vary with the extent of the disease, according with the published prospective randomized studies reported in Table 3 [9–11] or with the results of recent metanalysis which do not confirm advantages for the combination treatment [12]. From a QoL point of view, monotherapy with LH-RH analogues seems to be favored as a result of its minor toxicity [13].

In the intermittent androgen suppression (IAS), hormone therapy is periodically suspended in order to achieve a recovery of serum testosterone. In pre-clinical models, androgen recovery induced a re-maturation of prostate cancer cells to a pro-apoptotic stage (with consequent possible further apoptosis). As a consequence of multiple cycles of hormone therapy (apoptosis) and androgen recovery (re-maturation of cancer cells due to treatment suspension), one might obtain a delay in the time to progression to hormone-refractory status and an increased OS [14]. Other possible advantages are lower toxicity and therapy costs, increased QoL, related particularly to aspects of general well-being, emotional weakness, depression, asthenia and libido. In contrast with this optimistic view, one should remember that, until definitive results from the ongoing NCI-SWOG 9346 randomized prospective study are published, IAS has still to be considered an experimental approach.

Hormone-refractory prostate cancer (HRPC)

The incidence of HRPC has increased in the last years, also as a consequence of a higher percentage of patients with increasing PSA (biochemical progression) as the only manifestation of disease. Treatment options for HRPC are represented by second-line hormone therapies (antiandrogen withdrawal test, ketoconazole), chemotherapy (mitoxantrone- or estramustine-based chemotherapy) or best supportive care (BSC). There is no evidence of a survival benefit with second-line therapies, thus the primary end point of such treatments has to be QoL. A surrogate end point, such as PSA reduction, has been utilized in some phase II studies, due to the frequent absence of a measurable disease in advanced prostate cancer. QoL was evaluated in the randomized prospective EORTC phase III study 30865 comparing mitomycin-C with estramustine in 162 patients. A large number of problems were identified at baseline in 72 patients (doctor’s underestimation of symptoms, decreased functional status, pain, fatigue, psychological distress) but, possibly due to the low number of completed questionnaires (43), no differences
Table 3  Randomized studies comparing CAB with monotherapy

<table>
<thead>
<tr>
<th>Study</th>
<th>No. patients</th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT 0036 [9]</td>
<td>603</td>
<td>LH-RH ± flutamide</td>
<td>OS: CAB &gt; LH-RH (35.6 vs. 28.3 m) PFS: CAB &gt; LH-RH (16.5 vs. 13.9 m) QoL: Not measured</td>
</tr>
<tr>
<td>EORTC 30853 [10]</td>
<td>327</td>
<td>Orchiectomy vs. LH-RH+Flutamide</td>
<td>OS: CAB &gt; Orchiectomy (34.4 vs. 27.1 m) PFS: CAB &gt; Orchiectomy (30.7 vs. 19.6 m) QoL: Only 49 questionnaires completed</td>
</tr>
<tr>
<td>INT 0105 [11]</td>
<td>739</td>
<td>Orchiectomy ± Flutamide</td>
<td>OS: No difference (31 vs. 30 m) su 1387 pts PFS: No difference (21 vs. 18 m) QoL: Diarrhea, flutamide &gt; placebo (P = 0.001) Emotional function pl &gt; flut (P &lt; 0.003)</td>
</tr>
</tbody>
</table>

Table 4  Clinical results of mitoxantrone + prednisone vs. prednisone in 161 patients. a

<table>
<thead>
<tr>
<th></th>
<th>Mitoxantrone + prednisone</th>
<th>Prednisone</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>80</td>
<td>81</td>
</tr>
<tr>
<td>Clinical benefit (CB)</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>Median duration of CB</td>
<td>43 weeks</td>
<td>18 weeks</td>
</tr>
<tr>
<td>50% analgesic reduction</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>5</td>
<td>0</td>
</tr>
</tbody>
</table>

a Modified from Roila et al [17].

in QoL were observed, neither were differences in progression-free survival (PFS) or OS between treatment groups [15].

Recently a new end point, the so-called 'clinical benefit', evaluating some aspects of QoL has been used in some clinical trials on HRPC. In the first study, the efficacy of mitoxantrone plus prednisone was tested against prednisone alone in 161 patients with symptomatic HRPC. Pain decrease was the primary end point of the study, while secondary end points were a 50% reduction of analgesic consumption and an increase in PFS and OS. A concomitant complete evaluation of QoL with LASA (Linear Analogue Self Assessment) + PROSQUALI (Prostate Cancer Specific Quality of Life Instrument) and EORTC QLQ C30 questionnaires was made [16]. Chemotherapy showed increased pain control, physical activity or function, constipation and mood. Since these results (reported in Table 4) were confirmed as being significant by the complete QoL evaluation only for pain (a major problem in HRPC) and constipation (mood: P = 0.06), one doubts if the clinical benefit evaluation might substitute a complete evaluation of the QoL as a measure of treatment efficacy [35, 17].

Metastatic renal cell carcinoma (MRCC)

In the last 20 years, the increased use of ultrasound examinations, resulting in a higher detection rate of lower stage tumors, significantly lowered the incidence of MRCC at diagnosis. Treatment results for this refractory disease remain unsatisfactory. Possible treatment options for MRCC are immunotherapy with IFN-α (RR 12%), IL-2 (RR 18.6%), as a single agent or in combination, or best supportive care (BSC) in patients with unfavorable prognosis. The different immunotherapy options were recently compared in a prospective randomized study by Negrier et al. [18] with response rates ranging from 6.5%–7.5% with monotherapy to 18.6% with the combination of IFN-α and IL-2. Some long-term responders were observed.

A clear survival advantage has not been demonstrated for treatment over BSC. QoL should therefore be the primary end point in MRCC trials but, to date, there is only one study evaluating this aspect in MRCC [19]. In this study, the QoL of 20 patients with MRCC who underwent immunotherapy with TIL (tumor infiltrating lymphocytes) plus IL-2 was compared, retrospectively, with an established reference population with other chronic medical conditions or breast, prostate or other cancers. QoL was measured with RAND SF-36 and CARES-SF. Patients with MRCC reported a better health-related QoL compared to those with other malignancies but worse than the general population. As a consequence of this discomforting situation, patients with MRCC have to be placed, if possible, in clinical research protocols with QoL evaluation. Otherwise, options for the most appropriate treatment between immunotherapy or BSC could be driven by an analysis of the prognostic factors which correlate with survival (performance status, time from initial diagnosis, number and sites of metastases, nephrectomy and time from nephrectomy, weight loss) [20].

Bladder cancer

QoL in bladder cancer patients has not yet been fully studied: in advanced stages there are no studies having QoL as an end point, while in loco-regional disease there are very few data comparing QoL in patients undergoing conservative multidisciplinary treatments with radical surgery. Ethical committees should require that research protocols for advanced stage should analyze QoL as major end point, and trials comparing
conservative vs. radical approach should focus on the QoL dimensions.

Data about survival both with a conservative treatment or radical surgery in early stages of bladder cancer are similar [21]; some studies show that a conservative approach is feasible in 50% of patients [22], (mainly in stage T2, reaching a 10%–20% of clinical/pathological complete response after neo-adjuvant chemotherapy) [23].

A psychosocial analysis of patients who underwent radical cystectomy reports a perceived good quality of life in 95% of cases, sexual dissatisfaction in 47%, problems in the management of the ureterostomy in 30%, with variable levels of asthenia, difficulties in social relationships, and low degree of emotional distress [24]. It is important to underline that the conservative treatment is not free from side effects, such as hematological, gastrointestinal and renal toxicity [25]. As there is no absolute evidence for the best treatment choice, patients should be involved in the choice of the treatment options. There is evidence, in clinical practice, that a self-made decision can enhance disease and treatment compliance, and provide a greater satisfaction in the relationship with the medical and nursing staff.

Testicular cancer

The uro- oncological literature lacks studies regarding QoL related to the different treatment options. There are enough data on long-term toxicity effects in the large population of the cured patients. Although offering the same OS, treatment options for stage I differ very much in their impact on QoL. Arai reports a progressively worsening QoL in patients who underwent a wait-and-see approach [26]. On the other hand, chemotherapy causes long-term side effects (e.g. bleomycin pulmonary toxicity), higher incidence of secondary neoplasm, and a lower rate of fertility. Radiotherapy, as well, causes difficulties in erection, disorders in ejaculation, and secondary tumors [27]. Considering the ability to work, patients treated with chemotherapy have difficulties in concentration, low resistance to fatigue, and several problems related to the long-term side effects (neuropathy, Raynaud's syndrome, pulmonary fibrosis). Patients undergoing a wait-and-see approach seem to be less satisfied with their work than those who received chemotherapy. Sexual life may be influenced by psychological distress or by physical consequences of the illness and of the treatments. Such difficulties may take the form of endocrine disorders (hypoandrogenism), disorders in erection (angiosclerosis), ejaculatio sicca after retroperitoneal lymphnode dissection (RPLND), even more than three years after surgery [28].

Fertility may be compromised, and paternity rate may be 15%–30% lower than the general population, both because of a decreased desire of having children and because of an acquired infertility [29]. It is nowadays possible to preserve fertility using special techniques of radiotherapy and surgical procedures, or with a lower number and less toxic cycles of chemotherapy. Patients undergoing a wait-and-see approach have lower rates of paternity than those who had a RPLND; the former have more often alterations in the circadian rhythms than the latter, and a lower satisfaction in life and in sexual relationships [30].

QoL measurement

There are very few health-related QoL (HRQOL) measures specific to genitourinary cancer except the four instruments used for prostate cancer and the FACT-BI module for bladder cancer.

Prostate cancer module (QLQ-PR25) of the EORTC Quality of Life Questionnaire Core 30 Items (QLQ-C30) [31]

The prostate cancer module is a 25-item questionnaire intended for use by patients with localized and metastatic prostate cancer. It includes subscales assessing urinary symptoms (nine items), bowel symptoms (four items), treatment-related symptoms (six items) and sexual functioning (six items). The module is currently available in English, Dutch and French, and is being translated into a number of other European languages. The field testing of the prostate cancer module will take place in the context of the clinical trials of the EORTC Genito-Urinary Tract Cancer Cooperative Group, and other collaborating investigators.

FACT-P prostate cancer module (12 items) of the Functional Assessment of Cancer Therapy-General version (FACT-G) 27 items [32] (see Appendix 1)

The concurrent value of the FACT-P was confirmed by its ability to discriminate patients by disease stage, performance status, and baseline prostate-specific antigen (PSA) level. Sensitivity to change in performance status and PSA score over a two-month period suggested that some subscales of the FACT-Prostate (P) (including the PCS) are sensitive to meaningful clinical change [33].

The Prostate Cancer-Specific Quality-of-Life Instrument (PROSQOLI) (see Appendix 2)

The PROSQOLI is a short (10 items), simple, responsive measure of health-related QoL (HRQOL) in men receiving systemic treatment for advanced hormone-resistant prostate cancer. Convergent validity was assessed with the multivariate-multimethod matrix approach; discriminative validity was assessed according to conventional clinical criteria; and predictive validity was assessed by the ability to predict survival duration [16, 35].
The UCLA prostate cancer index (UCLA-PCI) (see Appendix 3)

The UCLA-PCI was developed by researchers at UCLA and RAND to measure health-related QoL (HRQOL) in patients treated for prostate cancer. It addresses general HRQOL and organ-targeted HRQOL. The index contains three parts: 1. RAND 36-Item Health Survey 1.0 (SF-36), 2. UCLA Prostate Cancer Index (20 items), and 3. Sociodemographic Items. The UCLA-PCI, with its six scales or domains, has demonstrated good psychometric properties and appeared to be well understood and easily completed. The high response among patients suggests that these men are especially interested in addressing both the general and disease-specific concerns that impact their daily QoL [34].

Conclusions

In the last decade, studies on QoL of genito-urinary cancer patients focused on problems arising from both disease- and treatment-related consequences, thus allowing us to better inform our patients and, in some cases, to suggest the potential benefit of palliative treatments (e.g., H.R. prostate Ca.). Unfortunately, none of the phase III trials had QoL as the main goal of the study. This has made it impossible, up to now, to give definitive answers to most of the problems still existing among the various options resulting in similar efficacy.

The increased awareness of QoL among patients and the recent increased number of comparative trials where QoL is the main goal of the study will certainly soon result in data with which we will be able to suggest a treatment option not only on the basis of a cost/efficacy ratio, but also in terms of the QoL impact on the neoplastic patient.

Appendix 1. Sample items from the FACT-P.

<table>
<thead>
<tr>
<th>Additional concerns</th>
<th>Not at all</th>
<th>A little</th>
<th>Somewhat</th>
<th>Quite a bit</th>
<th>Very much</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2 I am losing weight</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>C6 I have a good appetite</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P1 I have aches and pains that bother me</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>P2 I have certain areas of my body where I experience significant pain</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

Appendix 2. Sample items from the PROSQOL.

<table>
<thead>
<tr>
<th>Urinary problems</th>
<th>Worst I can imagine</th>
<th>No problems at all</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enjoying time with friends and family</td>
<td>Severely limited by illness or treatment</td>
<td>Not limited at all by illness or treatment</td>
</tr>
<tr>
<td>Mood</td>
<td>Very depressed</td>
<td>Not depressed at all</td>
</tr>
</tbody>
</table>

Appendix 3. Sample items from the UCLA-PCI.

22. How would you rate each of the following during the last four weeks? (Circle one number on each line)

<table>
<thead>
<tr>
<th>Very poor</th>
<th>Poor</th>
<th>Fair</th>
<th>Good</th>
<th>Very good</th>
</tr>
</thead>
</table>
a. Your level of sexual desire? | 1 | 2 | 3 | 4 | 5 |
b. Your ability to have an erection? | 1 | 2 | 3 | 4 | 5 |
c. Your ability to reach orgasm (climax)? | 1 | 2 | 3 | 4 | 5 |

References


Correspondence to:
E. Cortesi, MD
Medical Oncology
Dept. Experimental Medicine and Pathology
University of Rome 'La Sapienza'
Policlinico Umberto I
00161, Rome
Italy
E-mail: enrico.cortesi@uniroma1.it